WHAT IS CLAIMED:

1. A non-human mammal comprising a mutant GP IIIa gene wherein at least one of the two cytoplasmic tyrosine residues of the gene has been replaced with a non-tyrosine residue.

2. The non-human mammal of claim 1 wherein the non-tyrosine residue is phenylalanine.

3. The non-human mammal of claim 1 wherein the cytoplasmic tyrosine residues are tyrosine residues 747 and 759.

4. Platelets isolated from the blood plasma of the non-human mammal of claim 1.

5. The non-human mammal of claim 1 wherein the non-human mammal is selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

6. The non-human mammal of claim 5 wherein the non-human mammal is a mouse.

7. The non-human mammal of claim 1 wherein both cytoplasmic tyrosine residues have been replaced with a non-tyrosine residue.

8. The non-human mammal of claim 7 wherein the non-tyrosine residues are phenylalanine.

9. The non-human mammal of claim 7 wherein the cytoplasmic tyrosine residues are tyrosine residues 747 and 759.

10. Platelets isolated from the blood plasma of the non-human mammal of claim 7.

11. The non-human mammal of claim 7 wherein the non-human mammal is selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

12. The non-human mammal of claim 11 wherein the non-human mammal is a mouse.

13. A non-human mammal expressing a transgene stably introduced into its DNA, wherein the transgene comprises DNA encoding mutant GP IIIa wherein at least one of the two cytoplasmic tyrosine residues has been replaced with a non-tyrosine residue.

14. The non-human mammal of claim 13 wherein the non-tyrosine residue is phenylalanine.

15. The non-human mammal of claim 13 wherein the cytoplasmic tyrosine residues are tyrosine residues 747 and 759.

16. Platelets isolated from the blood plasma of the non-human mammal of claim 13.

17. The non-human mammal of claim 13 wherein the non-human mammal is selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

18. The non-human mammal of claim 17 wherein the non-human mammal is a mouse.

19. The non-human mammal of claim 13 wherein both cytoplasmic tyrosine residues have been replaced with a non-tyrosine residue.

20. The non-human mammal of claim 19 wherein the non-tyrosine residues are phenylalanine.

21. The non-human mammal of claim 19 wherein the cytoplasmic tyrosine residues are tyrosine residues 747 and 759.

22. Platelets isolated from the blood plasma of the non-human mammal of claim 19.

23. The non-human mammal of claim 19 wherein the non-human mammal is selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

24. The non-human mammal of claim 23 wherein the non-human mammal is a mouse.

25. A method of preparing a transformed non-human mammal with a mutant GP IIIa gene wherein at least one of the two tyrosine residues of the endogenous GP IIIa gene has been replaced with a non-tyrosine residue to prepare the mutant GP IIIa, said method comprising:

a) introducing into embryonic stem cells a nucleic acid molecule encoding the mutant GP IIIa gene;

b) regenerating a transformed non-human mammal from the cells resulting from step a).

26. The method of claim 25 wherein the non-tyrosine residue is phenylalanine.

27. The method of claim 25 wherein the cytoplasmic tyrosine residues are tyrosine residues 747 and 759.

28. The method of claim 25 wherein the non-human mammal is selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

29. The method of claim 28 wherein the non-human mammal is a mouse.

30. The method of claim 25 wherein both cytoplasmic tyrosine residues have been replaced with a non-tyrosine residue.

31. The method of claim 30 wherein the non-tyrosine residues are phenylalanine.

32. The method of claim 30 wherein the cytoplasmic tyrosine residues are tyrosine residues 747 and 759.

33. The method of claim 30 wherein the non-human mammal is selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

34. The method of claim 33 wherein the non-human mammal is a mouse.

35. The method of claim 25 further comprising breeding the transformed non-human mammal so as to produce a non-human mammal homozygotic for the mutant GP IIIa gene.

36. The method of claim 35 wherein the non-human mammal is a mouse.

37. A method of preparing a transformed non-human mammal with a mutant GP IIIa gene wherein at least one of the two tyrosine residues of the endogenous GP IIIa gene has been replaced with a non-tyrosine residue to prepare the mutant GP IIIa, said method comprising:

a) introducing into embryonic stem cells a nucleic acid molecule encoding the mutant GP IIIa gene and a selectable marker flanked by FRT sites;

b) identifying and selecting transformed cells;

c) removing the selectable marker from the transformed cells selected in step b) by transient transformation with FLP recombinase;

d) injecting the transformed cells from step c) into blastocysts; and,

e) regenerating a transformed non-human mammal from the blastocysts of step d), wherein the regenerated transformed non-human mammal is chimeric for the mutant GP IIIa gene.

38. The method of claim 37 wherein the non-tyrosine residue is phenylalanine.

39. The method of claim 37 wherein the cytoplasmic tyrosine residues are tyrosine residues 747 and 759.

40. The method of claim 37 wherein the non-human mammal is selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

41. The method of claim 37 wherein the non-human mammal is a mouse.

42. The method of claim 37 wherein both cytoplasmic tyrosine residues have been replaced with a non-tyrosine residue.

43. The method of claim 37 wherein the non-tyrosine residues are phenylalanine.

44. The method of claim 37 wherein the cytoplasmic tyrosine residues are tyrosine residues 747 and 759.

45. The method of claim 43 wherein the non-human mammal is selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

46. The method of claim 45 wherein the non-human mammal is a mouse.

47. The method of claim 37 further comprising breeding the transformed non-human mammal so as to produce a non-human mammal homozygotic for the mutant GP IIIa gene.

48. The method of claim 47 wherein the non-human mammal is a mouse.

49. The method of claim 37 further comprising the following steps:

f) breeding the chimeric non-human mammal with a wild-type non-human mammalto produce a non-human mammal heterozygotic for the mutant GP IIIa gene;

g) crossing a heterozygotic non-human mammal produced in step f) with a second heterozygotic non-human mammal produced in step f) ; and,

h) selecting a non-human mammal homozygotic for the mutant GP IIIa gene from the resulting progeny.

50. The method of claim 49 wherein the non-human mammal is a mouse.

51. A method comprising comparing a characteristic between two mammals of the same species, wherein one mammal has a wild-type GP IIIa gene and the other mammal has a mutant GP IIIa gene, wherein at least one of the two tyrosine residues of the wild-type GP IIIa gene has been replaced with a non-tyrosine residue in the mutant GP IIIa gene.

52. The method of claim 51 wherein the non-tyrosine residue is phenylalanine.

53. The method of claim 51 wherein the cytoplasmic tyrosine residues are tyrosine residues 747 and 759.

54. The method of claim 51 wherein the non-human mammal is selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

55. The method of claim 54 wherein the non-human mammal is a mouse.

56. The method of claim 51 wherein both cytoplasmic tyrosine residues have been replaced with a non-tyrosine residue.

57. The method of claim 56 wherein the non-tyrosine residues are phenylalanine.

58. The method of claim 56 wherein the cytoplasmic tyrosine residues are tyrosine residues 747 and 759.

59. The method of claim 56 wherein the non-human mammal is selected from the group consisting of sheep, goat, mouse, pig, dog, cat, monkey, chimpanzee, hamster, rat, rabbit, cow and guinea pig.

60. The method of claim 59 wherein the non-human mammal is a mouse.

61. The method of claim 51 further comprising comparing the bleeding time between the two mammal types.

62. The method of claim 51 further comprising comparing the thrombotic responses between the two mammal types.

63. The method of claim 51 further comprising comparing angiogenesis between the two mammal types.

64. The method of claim 51 further comprising comparing tumor metastasis between the two mammal types.

65. The method of claim 51 further comprising comparing inflammation between the two mammal types.

66. The method of claim 51 wherein the mammal is a mouse.

67. A method of determining the effect of an agent on a characteristic of a mammal that is attributable to the expression of the GP IIIa gene, said method comprising;

a) administering said agent to the mammal of claim 1;

b) maintaining said mammal for a desired period of time after said administration; and,

c) determining whether a characteristic of said mammal that is attributable to the expression of the mutant GP IIIa gene has been affected by the administration of said agent.

68. The method of claim 67 wherein the mammal is a mouse.

PCT

WO 99/53032
PCT/US99/08285

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From the INTERNATIONAL BUREAU

To:
ADLER, Reid, G.
Morgan, Lewis & Bockius LLP
1800 M Street, N.W.
Washington, DC 20036
ÉTATS-UNIS D'AMÉRIQUE

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 21 October 1999 (21.10.99)	
Applicant's or agent's file reference 44481-5043WO	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/US99/08285	15 April 1999 (15.04.99)	15 April 1998 (15.04.98)

Applicant
COR THERAPEUTICS, INC. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,EP,IL,JP,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GD,GE,GM,HR,HU,
   ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,
   SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   21 October 1999 (21.10.99) under No. WO 99/53032

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

Form PCT/IB/308 (July 1996)

2896979

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 01 December 1999 (01.12.99)	
International application No. PCT/US99/08285	**Applicant's or agent's file reference** 44481-5043WO
International filing date (day/month/year) 15 April 1999 (15.04.99)	**Priority date** (day/month/year) 15 April 1998 (15.04.98)
Applicant LAW, Deborah, Ann et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

15 November 1999 (15.11.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer R. Forax
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
./.		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/08285	15/04/1999	15/04/1998
International Patent Classification (IPC) or national classification and IPC C12N5/10		
Applicant COR THERAPEUTICS, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/11/1999	22.08.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Barnas, C Telephone No. +49 89 2399 7469

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/08285

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-22	as originally filed			

Claims, No.:

1-68	as received on	20/06/2000	with letter of	19/06/2000

Drawings, sheets:

1,2	as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

see separate sheet

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-68
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-68
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-50, 67, 68
	No:	Claims	51-66

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I

Basis of the report

The formulation "a mutant GPIIIa gene wherein at least one of the two ... tyrosine residues encoded by the ... gene has been replaced with a non-tyrosine residue", as used in amended claims 1, 25 and 37 is not clear and cannot be found in the application as originally filed. The same applies to the formulation "a mutant GPIIIa gene wherein at least one of the two tyrosine residues encoded by the wild-type GPIIIa gene has been replaced with a non-tyrosine residue encoded by the mutant GPIIIa gene", as used in amended claim 51. These formulations are, therefore, not directly and unambiguously derivable from the original application. Thus, said amendments do not meet the requirements of Art. 34 (2) PCT and have, therefore, been disregarded while establishing this report (Rule 70.2(c) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Art. 33 (2)(3) PCT, Novelty and Inventive Step

1.1. A non-human mammal expressing a transgene encoding mutant GP IIIa wherein at least one of the two cytoplasmic tyrosine residues has been replaced with a non-tyrosine residue, as claimed in claim 13, is not known from the cited prior art and cannot be derived therefrom in an obvious manner. Said claim and claims dependent thereon, i.e. **claims 13-24,** are, therefore, new and seem inventive.

1.2. Claim 1 seems to be directed to a non-human mammal comprising a mutant GP IIIa gene encoding a mutant GP IIIa protein wherein at least one of the two cytoplasmic tyrosine residues of the protein has been replaced with a non-tyrosine residue. Claims 25 and 37 seem to be directed to methods of preparing said non-human mammal by means of genetic engineering. Claim 51 seems to be directed to a method of comparing two mammals wherein one mammal has a mutant GP IIIa protein wherein at least one of the two tyrosine residues of the protein has been replaced with a non-tyrosine residue. Such mammals and methods are not known from the cited prior art and cannot be derived therefrom in an obvious manner. Said claim and claims dependent thereon, i.e. **claims 1-**

12 and 25-66, are, therefore, new and seem inventive (see, however, Re Item VIII, Art. 6 PCT, Lack of Clarity).

1.3. The same applies to a method of determining the effect of an agent on a characteristic that is attributable to the expression of the GP IIIa gene comprising administering said agent to the mammal of claim 1, as claimed in **claim 67**. Said claim and **claim 68** dependent thereon are, therefore, also new and seem inventive (see, however, Re Item VIII, Art. 6, Lack of Clarity).

2. Art. 33 (4) PCT, Industrial Applicability

Amended claim 51 embraces the mere comparison of a characteristic mediated by platalet function between two mammals wherein one of these mammals has a mutant GP IIIa gene. Claims 61-65 embrace the mere comparison of the bleeding time, the thrombotic responses, angiogenesis, tumour metastasis and inflammation of the two mammal types. The mere comparison of the two mammal types, however, does not represent a method applicable to the provision, improvement or testing of a product (for example a drug) or a process (for example the effect of a drug). Said claims and claims dependent thereon, i.e. **claims 51- 66**, are, therefore, not considered as susceptible of industrial application.

Re Item VIII
Certain observations on the international application

Art. 6 PCT, Lack of Clarity

Original claims 1, 25, 37 and 51 refer to "a mutant GP IIIa gene wherein at least one of the two ... tyrosine residues of the gene has been replaced with a non-tyrosine residue". A gene, however, consists of nucleotides and does not contain the amino acid tyrosine. The subject matter of said claims and claims dependent thereon, i.e. claims 1-12, 25-36, 37-50 and 51-66, is, therefore, not clearly defined (Art. 6 PCT). In view of the description of the present application, claims 1, 25, 37 and 51 have been examined as referring to "a mutant GP IIIa gene encoding a mutant GP IIIa protein wherein at least one of the two cytoplasmic tyrosine residues of the protein has been replaced with a non-tyrosine residue" (see claim 13).